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Description

This invention relates to an ion exchanger. More particularly, this invention is concerned with an ion exchanger which comprises: a totally porous matrix of an organic synthetic cross-linked copolymer comprising a skeleton and functional groups bonded to said skeleton, said matrix having fine pores distributed throughout the matrix; said ion exchanger further comprising alcoholic hydroxyl groups and ion exchange groups bonded to said matrix. The ion exchanger is useful as a liquid chromatography packing material to be employed in separating bio-substances which are present in an aqueous medium.

Various methods are known in the art to separate the components of body fluids such as urine and serum and cytosols, which are, for example, proteins, enzymes, peptides, amino acids, nucleotides or the like. Of the various methods, liquid chromatography especially gel permeation chromatography, in which an aqueous medium is advantageously utilized is more widely used in the fields of biochemistry, medicine and pharmacy since it provides multi-component information at one time by relatively simple operations. The gel permeation chromatography is advantageous in that it permits direct input of urine, serum or the like into the apparatus for analysis. However, gel permeation chromatography is not always suitable for separation of bio-substance components which have close molecular weights. Therefore, in recent years, attention is being drawn to liquid chromatography in which a packing material obtainable by incorporating ion exchange groups in the conventional gel permeation chromatography packing material is used to realize the combined effect of simplicity in operation characteristics of the gel permeation chromatography with excellent separating capacity due to the action of ion exchange groups.

Examples of prior art related to chromatographic gel materials which do not comprise ion-exchange groups are GB-A-2,034,328 and EP-A-0043074. The former document disloses a crosslinked polyvinyl alcohol gel comprising vinyl alcohol units and crosslinking units which comprise a triazine ring. The gel is obtained by copolymerizing a vinyl acylate and a crosslinking agent having a triazine ring and hydrolyzing the products. The latter document is concerned with similar gels, comprising vinyl alcohol units, vinylcarboxylate units, and crosslinking units which comprise a triazine ring. The gel is prepared by suspension copolymerization of a vinyl carboxylate and a crosslinking agent having a triazine ring and subjecting the resulting granular copolymer to a partial ester exchange reaction or saponification.

As a gel permeation chromatography packing material having ion exchange groups, there may be mentioned, for example, a granular polymer obtained by attaching ion exchange groups to a natural polymer such as agarose and dextran, usually cross-linked, and cellulose, as described in British Patent No. 936,039. The polymers disclosed in the British Patent have water regain values ranging between 1 and 50 g/g. The granular polymer is actually used for separation and analysis of bio-substances, such as proteins and enzymes. In this respect, reference may be made to Roger Epton, "Chromatography of Synthetic and Biological Polymers; vol. 2 Hydrophobic ion Exchange & Affinity Methods" pp. 73-127, Ellis Horwood Ltd., New York, 1978. However, these packing materials obtained from such natural polymers are generally called soft gels. The soft gels, in the wet state, are inferior in mechanical strength. Hence, these packing materials cannot be utilized in high-speed liquid chromatography in which the packing material must be small-sized granules yet strong in mechanical strength. As far as the inventor's knowledge extends, there is no generally accepted definition for the terminology "high speed". The criterion for the terminology varies with the granule diameter and column size. The term "high speed" used herein means about 1 ml/min or more with respect to the passing of a mobile phase in conducting chromatography, under a high pressure applied by a pump, using a column of several millimeters in inside diameter in which a packing material composed of granules with a size as small as 50 μm or less is charged. In this respect, reference may be made to J. J. Kirkland, "Modern Practice of Liquid Chromatography", John Wiley & Sons, New York, 1971.

As another example of known gel permeation chromatography packing materials having ion exchange groups, there may be mentioned derivatives of a copolymer of a monomer having a hydroxyl group, such as 2-hydroxyethyl methacrylate, and an alkylene glycol di(meth)acrylate, such as ethylene glycol dimethacrylate. These copolymer derivatives are disclosed in U.S. Patent No. 4,139,684. It is noted that in these copolymers, a hydroxyl group is bonded to a pendant group of the copolymer, and that hence, the hydroxyl group is not bonded directly to the skeleton of the matrix of the copolymer. The terminology "skeleton of the matrix" as used herein means a backbone structure of the matrix, which does not include functional groups, such as groups of the formula

$$-OH, -OCOCH_3, -OCH_2COOH, -OCH_2CH(OH)CH_2N(C_2H_5)_2, -OCH_2CH_2CH_2SO_3H$$

or the like. Although these copolymers give a packing material having a relatively high mechanical strength thereby to be useful for high-speed liquid chromatography, they have a drawback that they tend to disadvantageously adsorb thereto proteins, enzymes and other bio-substances non-specifically in an aqueous medium (hereinafter, this phenomenon is frequently referred to as "non-specific adsorption of bio-substances"). There-

fore, these copolymers are also limited in their applications. With respect to the characteristics of these copolymers, reference may be mode to Roger Epton, "Chromatography of Synthetic and Biological Polymers; vol. 1 Column Packings, GPC, GF and Gradient Elution" page 91, Ellis Horwood Ltd., New York, 1978.

As a further example of known gel permeation chromatography packing materials having ion exchange groups, there may be mentioned cation exchangers comprising a copolymer of styrene and divinylbenzene. It is noted that the copolymer is hydrophobic due to the absence of hydrophilic groups, such as hydroxyl groups. With respect to the copolymer, reference may be mode to K. Dorfner, "Ion Exchangers Properties and Applications", pp. 15-40. Ann. Arbor Science Publishers. Inc., Michigan. USA, 1972. Although the copolymer is excellent in mechanical strength and resistance to chemicals the use of the copolymer for nigh-speed chromatography of bio-substances is also limited since it disadvantageously tends to cause the above-mentioned non-specific adsorption of bio-substances.

As a still further example of known gel permeation chromatography packing materials having ion exchange groups, there may be mentioned an ion exchanger comprising silica gel and bonded thereto, ion exchange groups. This inorganic ion exchanger is disclosed in Japanese Patent Application Laid-Open Specification No. 55-66756/1980. Although this inorganic ion exchanger is excellent in mechanical strength, the use of the material for high-speed chromatography of bio-substances is very limited since its chemical stability, especially alkali resistance, is very low.

Therefore, there is still a strong demand in the art for a more useful ion exchanger that can be effectively utilized for high-speed chromatography of bio-substances.

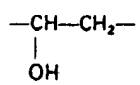
We have made intensive studies on the effect of polymer configuration, polymer components, functional groups and other factors on the performance of the resulting ion exchanger. As a result, it has unexpectedly been found that a totally porous organic synthetic crosslinked copolymer exhibiting a specific water regain value and a predetermined specific surface area and containing, in specific contents, hydroxyl groups and ion exchange groups gives an excellent ion exchanger which can be advantageously utilised for high-speed liquid chromatography of bio-substances. Based on this novel finding, we have completed this invention.

It is, therefore, an object of the present invention to provide a novel ion exchanger which is excellent in mechanical strength and resistance to chemicals and permits effective separation, by ion exchange, of bio-substances inclusive of low molecular electrolytes and proteins, thereby being advantageously utilized as a liquid chromatography packing material useful for separation of bio-substances, especially those which are present in an aqueous medium. The foregoing and other objects, features and advantages of the present invention will be apparent to those skilled in the art from the following detailed description and appended claims.

According to the present invention, there is provided an ion exchanger suitable for use as packing material for high-speed liquid chromatography, which comprises: a totally porous matrix of an organic synthetic crosslinked copolymer comprising a skeleton and function groups bonded to said skeleton, said matrix having fine pores distributed throughout the matrix; said ion exchanger further comprising alcoholic hydroxyl groups and ion exchange groups bonded to said matrix; characterized in that the alcoholic hydroxyl groups are bonded directly to said skelton; the content of said hydroxyl groups is in the range of 1.0 to 14.0 meq/g of the dry ion exchanger; and the content of said ion exchange groups bonded to said matrix is in the range of 0.02 to 5.0 meq/g of the dry ion exchanger, and wherein said ion exchanger has a water regain value of 0.5 to 4.0 g/g of the dry ion exchanger, a specific surface area, as measured by the B.E.T. method, of 5 to 1000 m^2/g of the dry ion exchanger, and a weight average granule size of 3 to 20 μm.

The ion exchanger of the present invention is totally porous. The terminology "totally porous" as used herein means that fine pores are distributed throughout the matrix of the ion exchanger.

In the ion exchanger of the present invention, alcoholic hydroxyl groups are bonded directly to the skeleton of a matrix of organic synthetic crosslinked copolymer An example of a matrix having alcoholic hydroxyl groups bonded directly to the skeleton thereof is one comprising vinyl alcohol monomer units By the terminology "vinyl alcohol monomer units" is meant moieties of the formula



In the present invention, it is essential that the content of alcoholic hydroxyl groups of the dry ion exchanger be in the range of 1.0 to 14.0 meq/g preferably 1.0 to 11.0 meq/g. The ion exchange having a hydroxyl group content of 1.0 to 14.0 meg/g exhibits hydrophilicity, and prevents hydrophobic adsorption of water-soluble substances thereto in an aqueous medium. The hydroxyl group content of 1.0 to 11.0 meq/g is more preferred from the viewpoint of minimizing the above-mentioned hydrophobic adsorption of water-soluble substances while

ensuring a high mechanical strength for the matrix. The content of alcoholic hydroxyl groups contained in the ion exchanger may be determined by reacting the hydroxyl groups with acetic anhydride in a pyridine solvent, measuring the amount of acetic anhydride consumed for the reaction with the hydroxyl groups or a weight change of the ion exchanger, and calculating from the resulting measured value. When 1 milli-mole of acetic anhydride is consumed for the reaction with 1 g of a dry ion exchanger, the content of alcoholic hydroxyl groups is 1 meq/g of the ion exchanger. It should be noted, however, that certain kinds of ion exchange groups also react with acetic anhydride. In such a case, the hydroxyl group content may be determined by subtracting the ion exchange group content determined in the later described manner from that calculated from the amount of acetic anhydride consumed.

The ion exchanger of the present invention has ion exchange groups bonded to the matrix. Suitable ion exchange groups to be used in the present invention are, for example, weakly acidic cation exchange groups such as carboxyl and phosphoric groups, weakly basic anion exchange groups such as primary, secondary and tertiary amino groups, strongly acidic cation exchange groups such as sulfonic groups, and strongly basic anion exchange groups such as quaternary ammonium salt groups. These ion exchange groups may be used either singly or in combination.

In the present invention, it is preferred that the content of ion exchange groups of the dry ion exchanger be in the range of 0.02 to 5.0 meq/g, especially 0.05 to 2.0 meq/g. The ion exchanger with an ion exchange group content of 0.02 to 5.0 meq/g exhibits various chemical properties due to the ion exchange groups, for example, ion exchanging or fractionation of water-soluble substances in an aqueous medium by ion exchange, while having a sufficient mechanical strength so that it is useful as a packing material for high-speed liquid chromatography. In the actual use, it is usually more preferable to employ on ion exchanger having an ion exchange group content of 0.05 to 2.0 meq/g. The content of ion exchange groups of the dry ion exchanger may be determined by various known methods that have been employed for the measurement of the exchange capacities of customary ion exchange resins. In this respect, reference may be made to K. Dorfner, "Ion Exchangers Properties and Applications", pages 40-44, Ann. Arbor Science Publishers, Inc., Michigan, U.S.A., 1972.

With respect to the ion exchanger of the present invention, the matrix comprises a totally porous organic synthetic crosslinked copolymer comprising a skeleton and functional groups bonded to the skeleton. The meaning of the terminology "skeleton" is as defined hereinbefore. The terminology "functional groups" as used herein meons any groups pendant to the skeleton such as, for example, those of the formulae

$-OCOCH_3$, $-OCOC_2H_5$, $-OCH_2COOH$, $-OCH_2CH(OH)CH_2(C_2H_5)_2$ and $-OCH_2CH_2CH_2SO_3H$.

The functional groups usually originate from the monomers subjected to copolymerization. However, they may be bonded to the skeleton of the copolymer after the copolymerization reaction. The structure of the matrix is not critical. However, it is preferred that the matrix comprises vinyl compound monomer units and crosslinkable monomer units. The matrix comprising vinyl compound monomer units and crosslinkable monomer units may be obtained by customary copolymerization of a vinyl compound monomer and a crosslinkable monomer, as described later. Any kind of vinyl compound monomer unit may be incorporated in the matrix of the ion exchanger of the present invention. Suitable examples of the vinyl compound monomer unit are those obtained from a vinyl carboxylate monomer, such as vinyl acetate, vinyl propionate, vinyl butyrate, vinyl valerate, vinyl pivalate and divinyl adipate. With respect to the crosslinkable monomer unit, also, any kind of crosslinkable monomer unit may be incorporated in the matrix of the ion exchanger of the present invention. Suitable crosslinkable monomer units are, for example, those obtained from a crosslinkable monomer having an isocyanurate ring, such as triallyl isocyanurate and diallyl isocyanurate, and from a crosslinkable monomer having a triazine ring, such as triallyl cyanurate. Suitable crosslinkable monomer units are also obtained from epichlorohydrin or a bisepoxy compound such as ethylene glycol diglycidyl ether, diethylene glycol diglycidyl ether and butane diol diglycidyl ether. These compounds may react with a hydroxyl group-containing compound to form a totally porous organic synthetic crosslinked copolymer. Of the above-cited crosslinkable monomer units, that from triallyl isocyanurate is particularly preferable because copolymerizability of triallyl isocyanurate with a vinyl carboxylate monomer is excellent, and because it gives a matrix having a good chemical resistance.

The ion exchanger of the present invention may preferably be such that with respect to a crosslinking index (X), it satisfies on inequality $0.05 \leqq X \leqq 0.4$. The terminology "crosslinking index" as used herein is defined by the formula:

$$X = \frac{nb}{a + nb}$$

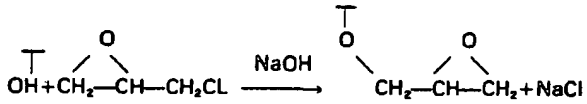
in which

a represents the molar fraction of the total monomer units minus the crosslinkable monomer units relative to the total monomer units constituting the matrix,

b represents the molar fraction of the crosslinkable monomer units relative to the total monomer units constituting the matrix, and

n represents the number of functional groups active in chain extension which are contained in a molecular of crosslinkable monomer that forms the crosslinkable monomer units upon polymerization.

In the above definition, the terminology "functional groups active in chain extension" mentioned with respect to the n means, for example, vinyl groups and epoxy groups. In the case of epihalohydrin, n is exceptionally 2, since the following reaction occurs therewith:



The ion exchanger with a crosslinking index of 0.05 to 0.4 has a sufficient mechanical strength as well as hydrophilicity due to non-ionic hydrophilic groups. The hydrophilicity due to non-ionic hydrophilic groups is needed to prevent undesirable interactions between the ion exchanger and the substances to be separated. When an especially high mechanical strength is needed as in the case of a packing material for high-speed liquid chromatography, it is preferred that the cross-linking index be in the range of 0.2 to 0.4.

To ensure both high separating capacity and high mechanical strength, it is requisite that the water regain value (W_R) of the ion exchanger according to the present invention be in an appropriate range. It is noted that the known ion exchanger from crosslinked agarose or crosslinked dextran, as mentioned hereinbefore, exhibits a high water regain value, and its mechanical strength, especially in the wet state, is very low. This trend is especially apparent when the pore size of the ion exchanger is large. The ion exchanger of the present invention has generally a water regain value of 0.5 to 4.0 g/g, preferably 0.5 to 3.0 g/g of the dry ion exchanger. The W_R value is the amount of water that can be contained in the pores of the ion exchanger when the ion exchanger is equilibrated with water, per unit weight of the ion exchanger in the dry state. In short, the W_R value can be a criterion indicating the quantity of pores within the ion exchanger. As the W_R value is increased, the weight of the skeleton-constituting portion of the ion exchanger in water namely, the weight of the ion exchanger per se, is relatively decreased. Accordingly, if the W_R value is too large, the mechanical strength of the ion exchanger is reduced. If the W_R value is too small, since the quantity of pores in the ion exchanger is reduced, the separating capacity of the ion exchanger is lowered. Therefore, from the viewpoint of the physical properties and separating capacity of the ion exchanger, it is preferable that the W_R value be within the above-defined range. The W_R value can be determined by subjecting an ion exchanger sufficiently equilibrated with distilled water to centrifugation to remove the water adhering to the surface of the ion exchanger, measuring the weight (W_1) of the ion exchanger, drying the ion exchanger, measuring the weight (W_2) of the ion exchanger after drying and calculating the W_R value according to the following formula:

$$W_R = \frac{W_1 - W_2}{W_2}$$

The ion exchanger of the present invention comprises a totally porous crosslinked copolymer which is rigid so that it has a large specific surface area in the dry state. In general, an organic synthetic polymer comprising a crosslinking structure is swollen in a solvent having affinity with the polymer, and shrinks in the dry state. In the soft gel, the pores filled with a solvent in the wet state are maintained only by the meshes in the network structure formed by cross-linking. Hence, in the case of the soft gel, the above-mentioned shrinkage is grave. The soft gel has a desired pore size when swollen in a solvent, but in the dry state, the soft gel shrinks so that the pores substantially disappear. When the pores substantially disappear, the specific surface area of the polymer comes to represent only the outer port of the polymer, which is usually less than 1 m^2/g. On the other hand, in the case of a totally porous crosslinked copolymer having a rigid structure, the pore size does not substantially vary whether the copolymer is in the swollen state or in the dry state. Its pores are so called permanent pores. The ion exchanger of the present invention generally has a specific surface area of 5 to 1000 m^2/g in the dry state. An ion exchanger having a specific surface area larger than 1000 m^2/g is disadvantageous in that its mechanical strength becomes poor. On the other hond, on ion exchanger having a specific surface area smaller than 5 m^2/g has a substantially uniform structure in which there are no significant amount of pores. Hence, such an ion exchanger cannot be suitably employed as a packing material for high-speed liquid

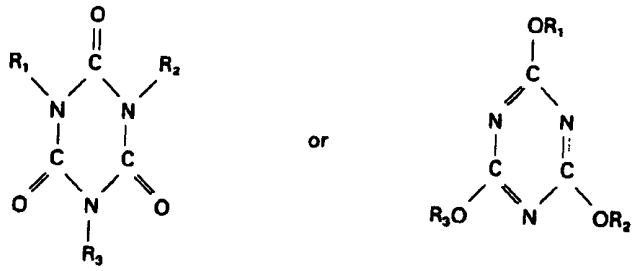
chromatography. Various methods are known for the determination of specific surface area. In the present invention, the specific surface area is determined according to the most popular BET method using nitrogen gas. The sample to be used for the determination of specific surface area should be sufficiently dried. However, since it is difficult to dry the ion exchanger of the present invention because of a high hydrophilic characteristic in order to determine the specific surface area, it is preferred that the ion exchanger be first equilibrated with acetone and then dried under reduced pressure at a temperature lower than 60°C.

The ion exchanger of the present invention has a granular form, especially a spherically granular form. In view of the intended use as a packing material for high-speed liquid chromatography, the weight average granule size of the invention ion exchanger is in the range of 3 to 20 μm, expecially 3 to 15 μm.

Now, a preferred mode of the process for the preparation of the ion exchanger of the present invention will be described. The process by which the ion exchanger of the present invention is prepared is by no means limited to the process described below.

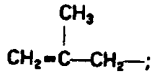
The ion exchanger of the present invention, for example, may be prepared by first copolymerizing a vinyl carboxylate monomer and a crosslinkable monomer to obtain a copolymer having ester group as functional groups, second converting the ester groups to hydroxyl groups by saponification or ester interchange reaction, and third effecting an ion exchange group incorporation reaction, as described later, to a predetermined percentage of the resulting hydroxyl groups taking advantage of the reactivity of the hydroxyl groups. The vinyl carboxylate monomer to be employed in this process may contain one or more polymerizable vinyl carboxylate groups. As the suitable vinyl carboxylate monomer, there may be mentioned, for example, vinyl acetate, vinyl propionate, vinyl butyrate, vinyl valerate, vinyl pivalate and divinyl adipate. There may be used either alone or in mixture. Of these vinyl carboxylate monomers, vinyl acetate, vinyl propionate and divinyl adipate are preferred, because of the ease in copolymerization, saponification or ester interchange reactions and lower cost.

The suitable crosslinkable monomer to be employed in this process is, for example, a compound of the formula:



or

wherein R_1, R_2 and R_3 each independently represent $CH_2=CH-CH_2-$, $CH\equiv C-CH_2-$ or



and any one of R_1, R_2 and R_3 may be a hydrogen atom.

Of the above monomers, triallyl isocyanurate having a structure in which all of the R_1, R_2 and R_3 groups of the above left-side formula are $-CH_2-CH=CH_2$ is most preferred as a crosslinkable monomer, because its copolymerizability with a vinyl carboxylate monomer is excellent, and because its stability against ester interchange or saponification is excellent.

The crosslinked copolymer comprising vinyl carboxylate monomer units and crosslinkable monomer units may be prepared by any of the customary polymerization techniques, such as suspension polymerization, bulk polymerization and emulsion polymerization. Of these polymerization techniques, suspension polymerization is preferred for the purpose of obtaining a copolymer to be used as a liquid chromatography packing material. In the above copolymerization of a vinyl carboxylate monomer and a crosslinkable monomer, a third monomer other than the above cited monomers may be added without any adverse effect on the physical properties of the ultimate ion exchanger.

When a copolymerization reaction of a vinyl carboxylate monomer and a crosslinkable monomer is effected, at least one organic solvent capable of dissolving the monomers may be added to the monomers to form a copolymer having permanent pores, as mentioned hereinbefore, and to control the porosity, pore size and

pore size distribution of the copolymer. As suitable organic solvents capable of dissolving such monomers, there may be mentioned, for example, aromatic hydrocarbons such as toluene and xylene; aliphatic hydrocarbons such as heptane, octane, cyclohexane and decalin; aliphatic esters, such as n-butyl acetate, isobutyl acetate, n-hexyl acetate and dioctyl adipate; aromatic esters, such as dimethyl phthalate, dioctyl phthalate and methyl benzoate; and alcohols such as butanol, heptanol and octanol. When suspension polymerization is effected, it may be preferable to use an organic solvent having little solubility in water. Usually, 20 to 300 parts by weight of such an organic solvent are added to 100 parts by weight of the monomers to be copolymerized. In the production of a copolymer to be used for preparation of an ion exchanger that is useful as a packing material for high-speed liquid chromatography which must have a high mechanical strength, it may be more preferable to add 30 to 100 parts by weight of the organic solvent to 100 parts by weight of the monomers.

To control the pore size and pore size distribution of the ultimate ion exchanger and/or to increase the flexibility of the ultimate ion echanger, either or both of a linear polymer and rubber which are soluble in the monomers may be added to the monomers. Suitably employed linear polymers and rubbers for the above purpose are, for example, polyvinyl acetate, polystyrene, chloroprene rubber and butadiene rubber. To 100 parts by weight of the monomers, 20 or less, preferably 10 or less parts by weight of such a linear polymer and/or rubber may be added to the monomers.

The kind and amount of the polymerization initiator to be employed in the above copolymerization reaction is not critical. They may be arbitrarily selected according to the copolymerization method employed. In the customary suspension polymerization or bulk polymerization, there may be used generally employable radical polymerization initiators, for example, azo type initiators such as 2,2'-azobisisobutyronitrile and 2,2'-azobis-(2,4-dimethylvaleronitrile), and peroxide type initiators such as benzoyl peroxide and lauroyl peroxide.

The saponification or ester interchange reaction of the resulting copolymer may be carried out using an acid or alkali in a solvent such as water, alcohols, or mixtures thereof. From the viewpoint of obtaining a packing material having a sufficient mechanical strength, it is preferred that the degree of saponification, namely the percentage of ester groups converted to hydroxyl groups relative to the total ester groups, be in the range of 10 to 80%. The degree of saponification may be controlled by optimizing the kind of solvent, temperature, time and other reaction conditions.

To the thus obtained copolymer having hydroxyl groups, ion exchange groups may be bonded, for example, in any of the following manners.

Carboxyl groups may be bonded to the copolymer by reacting a predetermined amount of hydroxyl groups of the copolymer with a dibasic acid anhydride such as succinic anhydride and glutaric anhydride, or a halogenated acetic acid such as monochloro acetic acid and monobromoacetic acid.

Sulfonic groups may be bonded to the copolymer by reacting a predetermined amount of hydroxyl groups of the copolymer with propanesultone, butanesultone, 1,3,2,4-dioxadithiane-2,2,4,4-tetraoxide or the like.

Primary amino groups, secondary amino groups and tertiary amino groups may be bonded to the copolymer by reacting a predetermined amount of hydroxyl groups of the copolymer with epichlorohydrin or a bisepoxy compound to form pendant epoxy groups and, subsequently, reacting the resulting epoxy groups with ammonio, ethylamine, diethylamine or the like. With respect to the incorporation of tertiary amino groups, it may alternatively be effected by reacting the hydroxyl groups with N-(2-chloroethyl)-diethylamine in alkali.

An anion exchanger having quaternary ammonium salt groups may be obtained by, for example, reacting on ion exchanger having tertiary amino groups with methyl iodide, methyl chloride or the like.

The amount of ion exchange groups bonded to the copolymer may be varied by varying the relative amounts of reactants and controlling the reaction conditions such as temperature and time.

The ion exchanger of the present invention may also be produced by the following method. A divinyl dicarboxylic ester such as divinyl adipate is polymerized and subjected to saponification in such a solvent as will not dissolve polyvinyl alcohol. The resulting polymer, in the above-mentioned solvent, is reacted with a compound having at least two functional groups which are capable of reacting with a hydroxyl group to form a covalent bond therebetween, such as epichlorohydrin and ethyleneglycol diglycidyl ether, thereby to obtain a crosslinked copolymer having vinyl alcohol units in which a hydroxyl group is bonded to a carbon atom of a vinyl monomer unit. Then, ion exchange groups may be incorporated into the thus obtained crosslinked copolymer in the manner as described hereinbefore to obtain on ion exchanger of the present invention.

The ion exchanger of the present invention is rigid and has on excellent mechanical strength. When the ion exchanger of the present invention is used as a packing material for liquid chromatography, an eluent can be passed at a high flow rate and, therefore, rapid analysis by liquid chromatography is possible.

Also, the ion exchanger of the present invention is stable in a wide pH range. Accordingly, the ion exchanger of the present invention can be employed, stably without any property change, under such an alkaline condition that, for example, a gel comprising a silica gel as its skeleton cannot be applied.

Further, the ion exchanger of the present invention has a sufficient hydrophilicity since it has a large amount

of hydroxyl groups. Hence, the ion exchanger of the present invention is advantageous in that it exhibits little hydrophobic adsorption of bio-substances, thereby being free from the disadvantageous non-specific adsorption of bio-substances.

The present invention will be explained in more detail with reference to the following Examples which should not be construed to be limiting the scope of the present invention.

Example 1

Into a three-necked round bottomed flask equipped with a reflux condenser, a nitrogen inlet tube and a stirrer and having a capacity of 3 liters were charged a homogeneous liquid mixture consisting of 100 g of vinyl acetate, 45.4 g of triallyl isocyanurate, 80 g of n-butyl acetate, 40 g of decalin and 3.4 g of 2,2'-azobisisobutyronitrile and 800 ml of water containing, dissolved therein, 1.0% by weight of polyvinyl alcohol and 0.2 M of sodium phosphate, and the resulting mixture was sufficiently stirred. Then, the mixture was heated at 65°C for 18 hours and at 75°C for 5 hours while stirring to effect suspension polymerization, so that a granular copolymer was obtained. The copolymer thus obtained was filtered, and washed with water and then with acetone so that the residual monomers and the organic solvent were extracted. The granular copolymer was, together with a solution consisting of 2 liters of methanol and 65 g of sodium hydroxide, put in a 5-liter three-necked flask equipped with a reflux condenser, a nitrogen inlet tube and a stirrer, followed by stirring at 15°C for 20 hours to saponify 55% of the ester groups of the copolymer to hydroxyl groups. The resulting saponified copolymer was filtered, washed with water and dried.

30 g of the obtained copolymer was charged in a 1000 ml three-necked flask equipped with a reflux condenser, a nitrogen inlet tube and a stirrer. Further, 300 ml of dimethyl sulfoxide, 50 ml of epichlorohydrin and 10 ml of a 30% by weight aqueous solution of sodium hydroxide were charged in the flask. The mixture was allowed to react at 30°C for 20 hours while stirring. The resulting gel was filtered, washed with water and subjected to suction filtration. The granular gel obtained by the suction filtration was then charged in a 1000 ml three-necked flask equipped with a reflux condenser, a nitrogen inlet tube and a stirrer. Subsequently 400 ml of a 10% by weight aqueous solution of diethylamine was put in the flask, and the mixture was allowed to react at 60°C for 5 hours while stirring. The resulting granular product was filtered, washed with water, and subjected to classification thereby to obtain a crosslinked copolymer having a hydroxyl group and a tertiary amino group as a weakly basic anion exchange group, namely, an anion exchanger. The anion exchanger had an average grain diameter of 9.0 microns.

The properties of the thus obtained anion exchanger were determined in the manners described hereinbefore. The anion exchanger had a hydroxyl group content of 4.8 meq/g of the dry anion exchanger, an ion exchange group content of 0.5 meq/g of the dry anion exchanger, a water regain value of 1.9 g/g of the dry anion exchanger and a specific surface area of 95 m^2/g of the dry anion exchanger.

The thus obtained anion exchanger was packed in a stainless steel column of 7.5 mm in inside diameter and 10 cm in length. Using the column, ovalbumin (molecular weight: 45,000) and α-chymotrypsinogen A (molecular weight: 27,000) were subjected to chromatographic analysis which was conducted under the following conditions:

Mobile phase: Aqueous solution (pH 7.5) containing 50 mM Tris-HCl buffer and 100 mM sodium chloride,
Flow rate of mobile phase: 2 ml/min,
Concentration of sample: 0.5% by weight,
Volume of sample: 100 µl, and
Column temperature: 30°C

It was found that the elution volumes of ovalbumin and α-chymotrypsinogen A were respectively 5.0 ml and 2.1 ml. With respect to the terminology "elution volume", it may also be referred to as "eluate volume" or "retention volume" in the art. Such a substantial difference in elution volume ensures complete separation of the two bio-substances. The complete separation was confirmed by chromatographic analysis of a mixture of the above-mentioned ovalbumin and α-chymotrypsinogen A solutions. The recovery of each of these bio-substances was more than 90%.

For the purpose of comparison, the above-mentioned saponified copolymer to which the anion exchange group was not yet bonded was packed in a stainless steel column of 7.5 mm in inside diameter and 10 cm in length, and the column was employed to conduct chromatographic analysis of ovalbumin and α-chymotrypsinogen A under the same conditions as mentioned above. The chromatogram showed that the elution volumes of ovalbumin and α-chymotrypsinogen A were 2.5 ml and 2.7 ml, respectively. Due to such a closeness in elution volume, these bio-substances could not be separated effectively.

Next, a 0.01 N aqueous NaOH solution was passed through the above-mentioned column packed with the anion exchanger at a flow rate of 1 ml/min at 30°C for 16 hours. The column was then employed to conduct

chromatographic analysis of ovalbumin and α-chymotrypsinogen A under the same conditions as mentioned above. The chromatogram showed that the elution volume of each of these bio-substances was substantially the same as that obtained prior to the passing of the 0.01 N aqueous NaOH solution. Their recoveries also did not change, and were determined to be more than 90% each. The anion exchanger was taken out from the column, and subjected to the measurements of the hydroxyl group content and the ion exchange group content. The values of hydroxyl group content and ion exchange group content remained substantially the same as those obtained prior to the passing of the NaOH solution. This substantiates that the anion exchanger according to the present invention is extremely stable in an alkaline solution.

In particular, as the pump for feeding the mobile phase, use was mode of "Hitachi 638-30" (model number of a pump manufactured and sold by Hitachi Ltd., Japan). As the detecter, use was mode of "Uvidec 100-N" (trade name of a detector manufactured and sold by Japan Spectroscopic Co., Ltd., Japan). The detection wavelength was 280 nm.

Example 2

An anion exchanger having a tertiary amino group as the anion exchange group was prepared in substantially the same manner as in Example 1 except that the amount of epichlorohydrin was changed to 90 ml. The resulting anion exchanger had an anion exchange group content of 1.02 meq/g of the dry anion exchanger, a hydroxyl group content of 4.6 meq/g of the dry anion exchanger, a water regain value of 2.1 g/g of the dry anion exchanger and a specific surface area of 72 m^2/g of the dry anion exchanger.

Examples 3 and 4

Saponified copolymers each having an epoxy group bonded thereto were prepared in substantially the same manner as in Example 1. The so-prepared copolymers were each reacted with ethylamine and ammonia under the reaction conditions as shown in Table 1, thereby obtaining anion exchangers having properties as indicated in Table 1.

Each of the above-obtained anion exchangers was packed in a stainless steel column of 7.5 mm in inside diameter and 10 cm in length, and used to conduct chromatographic analysis of ovalbumin and α-chymotrypsinogen A under substantially the same conditions as in Example 1. The elution volumes of ovalbumin and α-chymotrypsinogen A were as shown in Table 1.

From the results shown in Table 1, it is understood that ovalbumin and α-chymotrypsinogen A could be effectively separated.

On the other hand, in the same manner as in Example 1, a 0.01 N aqueous NaOH solution was passed through each of the columns packed with the above-obtained anion exchangers. After the passing of the aqueous NaOH solution, ovalbumin and α-chymotrypsinogen A were reanalyzed under the same conditions as in Example 1. The chromatogram showed that the elution volume of each of the bio-substances was substantially the same as that obtained prior to the passing of the 0.01 N aqueous NaOH solution. Each anion exchanger was then taken out from the column, and subjected to the measurements of the hydroxyl group content and the ion exchange group content. The values of hydroxyl group content and ion exchange group content remained substantially the same as those obtained prior to the passing of the NaOH solution.

TABLE 1

Example No.	Epoxy group-bonded polymer (g)	Reagent	Reaction conditions	Ion exchange group content (meq/g)	Hydroxyl group content (meq/g)	Water regain value (g/g)	Specific surface area (m^2/g)	Oval-bumin elution volume (ml)	α-chymo-trypsi-nogen elution volume (ml)
3	30	10% aqueous ethylamine solution (400 ml)	60°C/ 5 hours	0.52	5.4	1.9	110	4.5	2.2
4	30	10% aqueous ammonia solution (400 ml)	60°C/ 5 hours	0.58	5.2	1.9	56	4.0	2.1

Example 5

An anion exchanger having a tertiary amino group was prepared in substantially the same manner as in Example 1. The so-prepared anion exchanger had an anion exchange group content of 0.5 meq/g of the dry exchanger, a hydroxyl group content of 5.5 meq/g of the dry exchanger and a water regain value of 1.6 g/g of the dry exchanger. 30 g of the anion exchanger was charged in a 1000 ml three-necked flask equipped with a reflux condenser, a nitrogen inlet tube and a stirrer. Then, to the anion exchanger were added 300 ml of

acetone and 30 ml of methyl iodide. The mixture was allowed to react at 40°C for 20 hours while stirring, thereby obtaining an anion exchanger having a quaternary ammonium salt group. The thus obtained anion exchanger had an anion exchange group content of 0.5 meq/g of the dry anion exchanger, a hydroxyl group content of 4.9 meq/g of the dry anion exchanger, a water regain value of 1.9 g/g of the dry anion exchanger and a specific surface area of 70 m^2/g of the dry anion exchanger.

Example 6

A homogeneous liquid consisting of 100 g of vinyl acetate, 32.2 g of triallyl isocyanurate, 40 g of n-butyl acetate and 3.3 g of 2,2'-azobisisobutyronitrile was suspension polymerized and subjected to saponification reaction in substantially the same manner as in Example 1. 30 g of the obtained dry granular copolymer was reacted with epichlorohydrin in substantially the same manner as in Example 1. The reaction product was put in a three-necked flask having a capacity of 1000 ml and equipped with a reflux condenser, a nitrogen inlet tube and a stirrer and, to the product, 400 ml of a 10% by weight aqueous diethyl amine solution was added. While stirring, the mixture was allowed to react at 60°C for 5 hours. The granular product was filtered off, washed with water and subjected to classification to obtain an anion exchanger having an average grain diameter of 10.1 microns. The obtained anion exchanger had an anion exchange group content of 0.1 meq/g of the dry exchanger, a water regain value of 1.2 g/g of the dry exchanger and a specific surface area of 15 m^2/g of the dry exchanger. The hydroxyl group content of the dry anion exchanger was 9.0 meq/g.

Example 7

A homogeneous liquid mixture consisting of 100 g of vinyl acetate, 41.4 g of triallyl isocyanurate, 74 g of n-butyl acetate, 25 g of decane and 3.4 g of 2,2'-azobisisobutyronitrile was suspension polymerized and subjected to saponification reaction in substantially the same manner as in Example 1. 30 g of the obtained granular copolymer, together with 2.1 g of succinic anhydride, was added to 300 ml of pyridine, and heated while stirring at 60°C for 16 hours to obtain a cation exchanger having carboxyl groups. The obtained cation exchanger had a cation exchange group content of 0.13 meq/g of the dry exchanger, a hydroxyl group content of 5.5 meq/g of the dry exchanger, a water regain value of 1.59 g/g of the dry exchanger and a specific surface area of 87 m^2/g of the dry exchanger.

The thus obtained cation exchanger (designated *a* in Table 2) was packed in a stainless steel column of 7.5 mm in inside diameter and 25 cm in length. Using the column, standard protein samples were subjected to chromatographic analysis which was conducted under the following conditions:

Mobile phase: Aqueous solution (pH 7.0) containing 0.1 M sodium phosphate and 0.3 M sodium chloride,
Flow rate of mobile phase: 1 ml/min,
Volume of sample: 100 µl, and
Column temperature: 30°C.

For the purpose of comparison, a column containing a copolymer (designated *b* in Table 2) to which carboxyl incorporation reaction was not effected was also tested. As is apparent from the results shown in Table 2, when the above-obtained exchanger (a) was used, the elution volume of human serum albumin increased and the recovery of immunoglobulin was high, as compared with those when the copolymer (b) was used. These values remained almost unchanged even after the passing of a 0.01 N aqueous NaOH solution through the column at a flow rate of 1.0 ml/min at 30°C for 16 hours.

TABLE 2

Gel / Human serum protein	a		b	
	Elution volume (ml)	Recovery (%)	Elution volume (ml)	Recovery (%)
Immunoglobulin M	4.31	85	4.25	65
Haptoglobin	5.25	100	5.20	93
Immunoglobulin G	6.00	91	5.95	96
Transferrin	6.31	97	6.20	94
Albumin	10.44	86	8.00	91

Example 8

In substantially the same manner as in Example 7, a granular copolymer having hydroxyl groups was prepared by suspension polymerization and saponification reaction. 30 g of the granular copolymer was dispersed in 300 ml of an aqueous solution containing 4.5 g of chloroacetic acid and 7.4 g of sodium hydroxide, and heated at 30°C for 16 hours to obtain a cation exchanger having carboxyl groups. The obtained cation exchanger had a cation exchange group content of 1.0 meq/g of the dry exchanger, a hydroxyl group content of 4.6 meq/g of the dry exchanger, a water regain value of 1.60 g/g of the dry exchanger and a specific surface area of 64 m^2/g of the dry exchanger.

Example 9

A homogeneous liquid mixture consisting of 100 g of vinyl acetate, 32.2 g of trially isocyanurate, 40 g of n-butyl acetate and 3.3 g of 2,2'-azobisisobutyronitrile was suspension polymerized and subjected tosaponification reaction in substantially the same manner as in Example 1. 30 g of the obtained dry granular copolymer, together with 8.5 g of succinic anhydride, was added to 300 ml of pyridine, and heated at 60°C for 16 hours while stirring. The granular product was filtered off, washed with water and subjected to classification to obtain a cation exchanger having an overage grain diameter of 9.2 microns. The thus obtained cation exchanger had a water regain value of 1.02 g/g of the dry exchanger and a specific surface area of 28 m^2/g of the dry exchanger. The contents of hydroxyl group and carboxyl group of the dry cation exchanger were 8.9 meq/g and 1.02 meq/g,- respectively.

Example 10

A homogeneous liquid mixture consisting of 100 g of vinyl acetate, 41.4 g of triallyl isocyanurate, 70 g of n-butyl acetate and 3.4 g of 2,2'-azobisisobutyronitrile was suspension polymerized and subjected to saponification reaction in substantially the same manner as in Example 1. 30 g of the obtained dry granular copolymer having hydroxyl groups was put in a three-necked flask having a capacity of 1000 ml and equipped with a reflux condenser, a nitrogen inlet tube and a stirrer. Further, 300 ml of dimethyl sulfoxide, 5 g of 1,3-propanesultone and 20 ml of a 30% by weight aqueous sodium hydroxide solution were put in the flask, and the mixture was heated at 30°C for 20 hours while stirring. The granular product was filtered off, washed with water and subjected to classification to obtain a cation exchanger having sulfonic groups. The cation exchanger had an average grain diameter of 10.5 microns, a cation exchange group content of 0.5 meq/g of the dry exchanger, a water regain value of 1.2 g/g of the dry exchanger and a specific surface area of 65 m^2/g of the dry exchanger. The hydroxyl group content of the dry cation exchanger was 5.4 meq/g.

The thus obtained cation exchanger was packed in a stainless steel column of 7.5 mm in inside diameter and 10 cm in length. Using the column, myoglobin (molecular weight: 17000) and α-chymotrypsinogen A (molecular weight: 27000) were subjected to chromatographic analysis which was conducted under the following conditions:

Mobile phase: Aqueous solution (pH 6.0) containing 20 mM sodium phosphate and 100 mM sodium chloride,

Flow rate of mobile phase: 1.5 ml/min
Volume of sample: 100 µl, and
Column temperature: 30°C

The chromatogram showed that the elution volumes of myoglobin and α-chymotrypsinogen A were respectively 3.2 ml and 15.1 ml. Hence, they could be completely separated.

For the purpose of comparison, the above-mentioned saponified copolymer to which the cation exchange group was not yet bonded was packed in a stainless steel column with the above-mentioned size. The column was employed to conduct chromatographic analysis of myoglobin and α-chymotrypsinogen A under the same conditions as mentioned above. The chromatogram showed that the elution volumes of myoglobin and α-chymotrypsinogen A were respectively 3.3 ml and 2.8 ml. Due to such a closeness in elution volume, these bio-substances could not be separated effectively.

Next, a 0.01 N aqueous sodium hydroxide solution was passed through the above-mentioned column packed with the cation exchanger at a flow rate of 1 ml/min at 30°C for 16 hours. The column was then employed to conduct chromatographic analysis of myoglobin and α-chymotrypsinogen A under the same conditions as mentioned above. The chromatogram showed that the elution volume of each of these bio-substances was substantially the same as that obtained prior to the passing of the 0.01 N aqueous NaOH solution. Their recoveries also did not change, and were determined to be more than 90% each. The cation exchanger was taken out from the column, and subjected to the measurements of the hydroxyl group content and the cation exchange group content. The values of hydroxyl group content and cation exchanger group content remained substantially the same as those obtained prior to the passing of the NaOH solution. This substantiates that the cation exchanger according to the present invention is extremely stable in an alkaline solution.

In this Example, Hitachi 638 (model number of a pump manufactured and sold by Hitachi, Ltd., Japan) was used as the pump for feeding the mobile phase liquid. Uvidec 100-N (tradename of a detector manufactured and sold by Japan Spectroscopic Co., Ltd., Japan) was used as the detector, in which the detection wavelength employed was 280 nm.

Example 11

In substantially the same manner as described in Example 10, a cation exchanger having sulfonic groups was prepared except that instead of 5 g of 1,3-propanesultone and 20 ml of a 30% by weight aqueous sodium hydroxide solution, 15 g of propanesultone and 60 ml of a 30% by weight aqueous sodium hydroxide solution were respectively used. The obtained cation exchanger had a cation exchange group content of 1.35 meq/g of the dry exchanger, a water regain value of 1.3 g/g of the dry exchanger and a specific surface area of 91 m^2/g of the dry exchanger. The hydroxyl group content of the dry cation exchanger was 4.5 meq/g.

Example 12

A homogeneous liquid mixture consisting of 100 g of vinyl acetate, 32.2 g of trially isocyanurate, 40 g of n-butyl acetate and 3.3 g of 2,2'-azobisisosbutyronitrile was suspension polymerized and subjected to saponification reaction in the same manner as in Example 1. 30 g of the obtained dry granular copolymer was put in a three-necked flask having a capacity of 1000 ml and equipped with a reflux condenser, a nitrogen inlet tube and a stirrer. Further, 300 ml of dimethyl sulfoxide, 2 g of 1,3-propanesultone and 5 ml of a 30% by weight aqueous sodium hydroxide solution were put in the flask, and the mixture was heated at 30°C for 20 hours while stirring. The obtained granular product was filtered off, washed with water and subjected to classification to obtain a cation exchanger having an average grain diameter of 9.1 microns. The obtained cation exchanger had a cation exchange group content of 0.1 meq/g of the dry exchanger, a water regain value of 1.2 g/g of the dry exchanger and a specific surface area of 12 m^2/g of the dry exchanger. The hydroxyl group content of the dry cation exchanger was 9.0 meq/g.

Claims

1. An ion exchanger suitable for use as a packing material for high-speed liquid chromatography, which comprises:

a totally porous matrix of an organic synthetic crosslinked copolymer comprising a skeleton and functional groups bonded to said skeleton, said matrix having fine pores distributed throughout the matrix; said ion exchanger further comprising alcoholic hydroxyl groups and ion exchange groups bonded to said matrix, characterized in that the alcoholic hydroxyl groups are bonded directly to said skeleton; the content of said hyd-

roxyl groups is in the range of 1.0 to 14.0 meq/g of the dry ion exchanger; and

the content of said ion exchange groups bonded to said matrix is in the range of 0.02 to 5.0 meq/g of the dry ion exchanger, and

wherein said ion exchanger has a water regain value of 0.5 to 4.0 g/g of the dry ion exchanger, a specific surface area, as measured by the B.E.T. method, of 5 to 1000 m^2/g of the dry ion exchanger, and a weight average granule size of 3 to 20 μm.

2. An ion exchanger according to Claim 1, wherein said copolymer comprises vinyl compound monomer units and crosslinkable monomer units.

3. An ion exchanger according to Claim 2, wherein said hydroxyl groups are bonded to carbon atoms of repeating units of the formula

$$-CH_2-\underset{|}{CH}-.$$

4. An ion exchanger according to any one of Claims 1 to 3, wherein said ion exchange groups are at least one member selected from the class consisting of weakly acidic cation exchange groups, weakly basic anion exchange groups, strongly acidic cation exchange groups and strongly basic anion exchange groups.

5. An ion exchanger according to any one of Claims 1 to 4, wherein said ion exchange groups are at least one member selected from the class consisting of carboxyl groups, phosphoric groups, primary amino groups, secondary amino groups, tertiary amino groups, sulfonic groups and quaternary ammonium salt groups.

6. An ion exchange according to any one of Claims 2 to 5, wherein said matrix has a crosslinking index (X) in the range satisfying an inequality $0.05 \leq X \leq 0.4$,

said crosslinking index (X) being defined by the formula

$$\frac{nb}{a + nb}$$

in which

a represents the molar fraction of the total monomer units minus the crosslinkable monomer units relative to the total monomer units constituting the matrix,

b represents the molar fraction of the crosslinkable monomer units relative to the total monomer units constituting the matrix, and

n represents the number of functional groups active in chain extension which are contained in a molecule of crosslinkable monomer that forms the crosslinkable monomer units upon polymerization.

7. An ion exchanger according to any one of Claims 2 to 6, wherein each of said crosslinkable monomer units contains an isocyanurate ring or triazine ring.

8. An ion exchanger according to any one of Claims 3 to 7, wherein the content of the hydroxyl groups, contained in the vinyl alcohol monomer units, is in the range of 1.0 to 11.0 meq/g of the dry ion exchanger.

9. An ion exchanger according to any one of Claims 1 to 7, wherein the content of the ion exchange groups is in the range of 0.05 to 2.0 meq/g of the dry ion exchanger.

10. An ion exchanger according to any one of Claims 1 to 9, wherein the ion exchanger has a water regain value of 0.5 to 3.0 g/g of the dry ion exchanger.

Revendications

1. Echangeur d'ions qui convient en vue d'être utilisé comme matériau de garnissage pour une chromatographie en phase liquide à grande vitesse et qui comprend :
une matrice entièrement poreuse en un copolymère organique synthétique réticulé comprenant un squelette et des groupes fonctionnels liés au squelette, la matrice ayant des pores fins répartis dans toute la matrice ; cet échangeur d'ions comprenant en outre des groupes hydroxyle alcooliques et des groupes d'échange d'ions liés à la matrice ; caractérisé en ce que
   - les groupes hydroxyle alcooliques sont liés directement au squelette ; la teneur en ces groupes hydroxyle est de l'ordre de 1,0 à 14,0 meq/g de l'échangeur d'ions sec ; et
   - la teneur en les groupes d'échange d'ions liés à la matrice est de l'ordre de 0,02 à 5,0 mq/g de l'échangeur d'ions sec, et
   - l'échangeur d'ions a un taux de réabsorption de l'eau de 0,5 à 4,0 g/g de l'échangeur d'ions sec, une surface spécifique, telle que mesurée par la méthode B.E.T., de 5 à 1000 m^2/g de l'échangeur d'ions sec et une dimension moyenne en poids des granules de 3 à 20 μm.

2. Echangeur d'ions suivant la revendication 1, dans lequel le copolymère comprend- des motifs de monomère vinylique et des motifs de monomère réticulable.

3. Echangeur d'ions suivant la revendication 2, dans lequel les groupes hydroxyle sont liés à des atomes de carbone de motifs récurrents de formule $-CH_2-CH-$.

4. Echangeur d'ions suivant l'une quelconque des revendications 1 à 3, dans lequel les groupes d'échange d'ions sont au moins un élément choisi parmi les groupes d'échange de cations faiblement acides, les groupes d'échange d'anions faiblement basiques, les groupes d'échange de cations fortement acides, et les groupes d'échange d'anions fortement basiques.

5. Echangeur d'ions suivant l'une quelconque des revendications 1 à 4, dans lequel les groupes d'échange d'ions sont l'un au moins des éléments choisis parmi les groupes carboxyle, les groupes phosphoriques, les groupes amino primaires, les groupes amino secondaires, les groupes amino tertiaires, les groupes sulfoniques et les groupes de sels d'ammonium quaternaires.

6. Echangeur d'ions suivant l'une quelconque des revendications 2 à 5, dans lequel la matrice a un indice de réticulation qui satisfait à l'inégalité $0,05 \leq X \geq 0,4$,

cet indice de réticulation (X) étant défini par la formule :

$$X = \frac{nb}{a + nb}$$

dans laquelle

a représente le rapport molaire de tous les motifs de monomères diminués des motifs de monomères réticulables à tous les motifs de monomères constituant la matrice,

b représente le rapport molaire de tous les motifs de monomères réticulables à tous les motifs de monomères constituant la matrice, et

n représente le nombre de groupes fonctionnels actifs dans l'extension de chaîne, qui sont contenus dans une molécule de monomère réticulable qui forme les motifs de monomères réticulables après polymérisation.

7. Echangeur d'ions suivant l'une quelconque des revendications 1 à 6, dans lequel chaque motif monomère réticulable contient un cycle isocyanurate ou un cycle triazine.

8. Echangeur d'ions suivant l'une quelconque des revendications 3 à 7, dans lequel la teneur en les groupes hydroxyle contenus dans les motifs de monomère alcool vinylique est de l'ordre de 1,0 à 1,0 meq/g de l'échangeur d'ions sec.

9. Echangeur d'ions suivant l'une quelconque des revendications 1 à 7, dans lequel la teneur en les groupes d'échange d'ions est de l'ordre de 0,05 à 2,0 meq/g de l'échangeur d'ions sec.

10. Echangeur d'ions suivant l'une quelconque des revendications 1 à 9, dans lequel l'échangeur d'ions a un taux de réabsorption de l'eau de 0,5 à 3,0 g/g de l'échangeur d'ions sec.

Patentansprüche

1. Ionenaustauscher, der zur Verwendung als Packungsmaterial für die Schnell-Flüssigkeitschromatographie geeignet ist und umfaßt:

eine vollständig poröse Matrix aus einem organischen synthetischen vernetzten Copolymer, welches ein Gerüst und an dieses Gerüst gebundene funktionelle Gruppen enthält, wobei die Matrix feine Poren aufweist, die in der gesamten Matrix verteilt sind, der Ionenaustauscher außerdem an die Matrix gebundene alkoholische Hydroxylgruppen und Ionenaustauschgruppen aufweist, dadurch gekennzeichnet, daß

die alkoholischen Hydroxylgruppen direkt an das Gerüst gebunden sind, der Gehalt dieser Hydroxylgruppen im Bereich von 1,0 bis 14,0 mÄq/g, bezogen auf den trockenen Ionenaustauscher, liegt; und

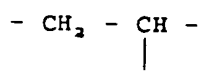
der Gehalt der an die Matrix gebundenen Ionenaustauschgruppen im Bereich von 0,02 bis 5,0 mÄq/g, bezogen auf den trockenen Ionenaustauscher, liegt, und

wobei der Ionenaustauscher einen Wasser-Rückhaltewert von 0,5 bis 4,0 g/g, bezogen auf den trockenen Ionenaustauscher, und eine spezifische Oberfläche, gemessen nach der B.E.T.-Methode, von 5 bis 1000 m^2/g, bezogen auf den trockenen Ionenaustauscher, und ein Gewichtsmittel der Korngröße von 3 bis 20 µm

aufweist.

2. Ionenaustauscher gemäß Anspruch 1, worin das Copolymer Monomereinheiten einer Vinylverbindung und vernetzbare Monomereinheiten enthält.

3. Ionenaustauscher gemäß Anspruch 2, worin die Hydroxylgruppen an Kohlenstoffatome von wiederkehrenden Einheiten der Formel



gebunden sind.

4. Ionenaustauscher gemäß einem der Ansprüche 1 bis 3, worin die Ionenaustauschgruppen mindestens ein Mitglied aus der Klasse der schwach-sauren Kationenaustauschgruppen, der schwach-basischen Anionenaustauschgruppen, der stark sauren Kationenaustauschgruppen und der stark-basischen Anionenaustauschgruppen sind.

5. Ionenaustauscher gemäß einem der Ansprüche 1 bis 4, worin die Ionenaustauschgruppen mindestens ein Mitglied aus der aus Carboxylgruppen, Phosphorsäuregruppen, primären Aminogruppen, sekundären Aminogruppen, tertiären Aminogruppen, Sulfonsäuregruppen und quaternären Ammoniumsalzgruppen bestehenden Klasse sind.

6. Ionenaustaucher gemäß einem der Ansprüche 2 bis 5, worin die Matrix einen Vernetzungs-Index (X) in dem Bereich hat, welcher der Ungleichung $0{,}05 \leqq X \leqq 0{,}4$ genügt, wobei der Vernetzungsindex (X) durch die folgende Formel definiert ist

$$\frac{nb}{a + nb}$$

in der

a die molare Fraktion von Gesamtmonomereinheiten minus vernetzbare Monomereinheiten im Verhältnis zu den Gesamtmonomereinheiten, welche die Matrix bilden, bedeutet,

b die molare Fraktion von vernetzbaren Monomereinheiten, im Verhältnis zu den Gesamtmonomereinheiten, welche die Matrix bilden, bedeutet und

n die Anzahl von funktionellen Gruppen darstellt, die bei der Kettenverlängerung wirksam sind, welche in einem Molekül eines vernetzbaren Monomeren enthalten sind, welches bei der Polymerisation die vernetzbaren Monomereinheiten ausbildet.

7. Ionenaustauscher gemäß einem der Ansprüche 2 bis 6, worin jede dieser vernetzbaren Monomereinheiten einen Isocyanuratring oder Triazinring enthält.

8. Ionenaustauscher gemäß einem der Ansprüche 3 bis 7, worin der Gehalt an Hydroxylgruppen, die in den Vinylalkohol-Monomereinheiten vorhanden sind, im Bereich von 1,0 bis 11,0 mÄq/g, bezogen auf den trockenen Ionenaustauscher, liegt.

9. Ionenaustauscher gemäß einem der Ansprüche 1 bis 7, worin der Gehalt der Ionenaustauschgruppen im Bereich von 0,05 bis 2,0 mÄq/g, bezogen auf den trockenen Ionenaustauscher, liegt.

10. Ionenaustauscher gemäß einem der Ansprüche 1 bis 9, wobei der Ionenaustauscher einen Wasser-Rückhaltewert von 0,5 bis 3,0 g/g, bezogen auf den trockenen Ionenaustauscher, hat.